DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 2 1999

1305 '99 SEP -7 P1:52

Thomas J. Donegan, Jr.
Vice President-Legal & General Counsel
The Cosmetic, Toiletry, and Fragrance Association
1101 17th Street, N.W., Suite 300
Washington, D.C. 20036-4702

Re: Docket No. 78N-0038

Dear Mr. Donegan:

This letter concerns our July 22, 1999 public meeting on the over-the-counter (OTC) sunscreen drug product final monograph (published on May 21, 1999, 64 FR 27666). At that meeting, we indicated that written feedback would be forthcoming to further clarify the agency's concerns about the determination of high sun protection factor (SPF) values and how this information can be communicated to the consumer in sunscreen product labeling.

As you are aware, the completion of regulations for OTC sunscreen products within a specified time period was mandated by section 129 of the Food and Drug Administration Modernization Act (FDAMA) of 1997. As you are also aware (Docket 78N-0038, Comment CP 11), Congress recognized that various technical and scientific issues may take longer to resolve than other aspects of the rulemaking and did not intend that all regulation in this area be complete or comprehensive by a specified date. Therefore, the agency proceeded to complete the tentative final monograph for OTC sunscreen drug products except for certain testing issues and ultraviolet A (UVA) radiation labeling that require the submission and evaluation of additional data and, as appropriate, further notice and comment rulemaking.

While the agency believes that the sunscreen final monograph test procedures for measuring SPF values up to 30 represents at this time a straightforward, well-understood, and sound method for measuring these values, a number of comments received by the agency questioned the ability of current testing methods to accurately and reproducibly determine SPF values for high-SPF sunscreen products (64 FR 27666 at 27680). Most of these concerns related to potential interlaboratory variation when utilizing SPF test methodology for such products. Primary concerns included the potential for overestimation of high SPF values due to the spectra of currently used solar simulators and the need for one or more high-SPF standard sunscreens (i.e., as laboratory controls). Long radiation exposures necessitated by SPF values well above 30 and the use of a relatively low-SPF laboratory control may significantly increase the potential for decreased interlaboratory accuracy and reproducibility for high-SPF sunscreen drug products. These and other comments (see below) raised useful ideas for proposed improvements to the SPF testing procedures.

78N-0038

ANS 6

The following items represent areas of concern about the adequacy of current SPF test procedures specifically for the determination of high SPF values. We would appreciate receiving your comments on these issues with appropriate supporting data, as applicable:

1. Solar Simulator Spectral Power Distribution - The agency has received requests, including a recent citizen petition (Docket 78N-0038, Comment CP12), suggesting the adoption of a spectral power distribution that specifies the proportion of erythema-effective radiation in a table format. It was suggested that the spectra of currently used solar simulators (especially around 290 nanometers (nm) and above 350 nm) could cause overestimation of SPF values for high SPF sunscreens. Because shorter wavelengths can make a very large contribution to erythema, small errors in the 290 nm region of solar simulator spectra can have considerable effects. Also, spectral power deficiencies above 350 nm may give artificially high SPF values for sunscreen drug products that absorb poorly in the long wavelength UVA region. Comments have suggested that the agency replace the "sun at a zenith angle of 10°" and "less than 1 percent shorter than 290 nm" specifications in § 352.71 of the sunscreen monograph with the European Cosmetic, Toiletry, and Perfumery Association (COLIPA) table of "percent erythemal contribution" as the spectral power distribution standard for the light source used in the SPF test procedures.

Previous comments submitted by your association (Docket 78N-0038, Comment C361) indicated concurrence with solar simulator spectral distribution specifications similar to those contained in the COLIPA standard. We would be interested in knowing if your association remains in concurrence. The Division of OTC Drug Products ("the Division") would also appreciate your comments concerning a potential modification of the standard that would modify the erythema-effective radiation contribution of wavelengths below 290 nm to less than 0.1 percent (to prevent overestimation of SPF values). We believe that this specification is readily obtainable with commercially available 320 nm cut-off filters. In addition, we are interested in your comments concerning the practicality of lowering the below-290 nm specification to 0.01 percent. Therefore, a solar simulator using the modified COLIPA standard for determining the SPF of a sunscreen drug product would be filtered so that it provides a continuous emission spectrum from 290 to 400 nm with the following percentage of erythema-effective radiation in each specified range of wavelengths:

SOLAR SIMULATOR EMISSION SPECTRUM

Wavelength range (nanometers)	Percent erythemal contribution
< 290	< 0.1
290-310	46-67
290-320	80-91
290-330	86.5-95
290-340	90.5-97
290-350	93.5-99

2. Thermal Overloading of the Skin - The testing of high-SPF sunscreens necessitates longer exposure times than testing of lower SPF values. Such increases in irradiance levels have the potential to produce thermal overloading of the skin and influence the ultraviolet (UV) radiation dose reciprocity relationship (and therefore SPF values). It has been suggested that limits such as 1250 to 1500 watts/meter^2 be placed on the total irradiance delivered to the skin for all wavelengths. Information received by the agency, including a recent citizen petition (Docket 78N-0038, Comment CP12), also suggests that the "out of band" specification in § 352.71 of the sunscreen monograph (i.e., that not more than 5 percent of a solar simulator's total energy output can be contributed by wavelengths longer than 400 nm) is not obtainable from many devices currently utilized for evaluating sunscreens.

The Division considers it important to limit total energy delivered to the skin so that skin temperature does not reach a point that influences the UV dose reciprocity relationship when encountering the long exposure times necessary to test high SPF sunscreens. We believe replacing the "out of band" specifications in § 352.71 with a limit on total solar simulator irradiance for all wavelengths may be an appropriate modification of current testing procedures that will improve the testing of high-SPF sunscreens. Previous comments submitted by your association (Docket 78N-0038, Comment C361) indicated concurrence with a total irradiance limit of 1500 watts/meter^2 for all wavelengths. We would be interested in knowing if your association remains in concurrence with this limit and your comments on a limit of 1250 watts/meter^2.

3. High-SPF Standard Sunscreen - The agency received several suggestions that standard sunscreens (i.e., controls) with SPF values of 15 or higher be developed for the testing of high-SPF sunscreen drug products. Although data submitted to the agency tend to support the conclusion that a specific control(s) may be needed to accurately test high-SPF products, study results from single laboratories are not sufficient. The studies did not include sufficient numbers of subjects, did not address suitability of a standard across different laboratories, and did not

document the following properties required in a standard sunscreen: (1) Low level of interlaboratory variation, (2) sensitivity to experimental error, and (3) ease of preparation with a reasonable degree of accuracy.

The CTFA previously supplied "round-robin," collaborative SPF testing data from seven laboratories on 153 subjects, with two possible SPF 15 standard sunscreen preparations, "Formulation A" and "Formulation B" (Docket 78N-0038, Comments C111 and RPT7). Your association concluded that "Formulation B was preferred due to its less complex formula and slightly more consistent results."

The Division believes that the data submitted by the CTFA could support "Formulation B" as an appropriate SPF 15 standard sunscreen if additional information is submitted and found acceptable. Because the formulation was supplied to all laboratories by a single source, there are no data to demonstrate that multiple laboratories can prepare, assay, and utilize the standard successfully. Further, the standards were not analyzed by the spectrophotometric method in § 352.70(c) of the sunscreen monograph, but rather by an alternate proposed method (see below for details concerning that alternate method and the additional required data). We invite submission of the additional data necessary to document the suitability of the requested standard sunscreen and the analytical method. Also, it would be helpful to submit information on a standard sunscreen (excluding data) under the headings listed in § 352.70(a), (b), (c)(1), (c)(2), (c)(3), (c)(4), and (c)(5), as applicable.

In addition, we would appreciate your comments and any supporting data concerning the need for additional standard sunscreens (with SPF values higher than 15) as well as the use of specific standard sunscreens for specific SPF ranges (i.e., bracketing).

4. High-Performance Liquid Chromatography (HPLC) Assay - As discussed above, data supplied by the CTFA in support of an SPF 15 standard sunscreen included the use of an HPLC assay instead of the spectrophotometric assay in § 352.70(c). It was suggested that the HPLC protocol is now commonly used by analytical laboratories for the assay of sunscreen formulations (and that it can also be used for the HMS standard sunscreen).

Before we can evaluate the HPLC method supplied with the SPF 15 standard sunscreen data, method validation data will be required. The validation package must document specificity, accuracy, limit of detection, linearity, precision, and reproducibility of the method. We are especially concerned that the presence of any impurities in the standard sunscreen and product formulations can be detected by the HPLC method (particularly UV radiation-absorbing impurities), because interfering substances could affect the SPF determination. The validation package should include chromatograms and must demonstrate that the HPLC method is suitable for both the SPF 4 (HMS) and SPF 15 standards (or other standard sunscreens if appropriate). The chemistry guideline "Reviewer Guidance, Validation of Chromatographic Methods"

explains these requirements in greater detail and is available on the agency's Internet website for the Center for Drug Evaluation and Research (http://www.fda.gov/cder/guidance/index.htm), or may be obtained from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

5. Number of Test Subjects – It has been suggested that the "limitation" of 20 to 25 subjects in the SPF test (§ 352.72(g)) may be an issue for sunscreen drug products with high SPF values due to potential for high variability in the responses obtained. The Division would be interested in receiving any data on the testing of SPF values over 30 in relation to this issue and suggestions for an appropriate number of test subjects to be used in such testing.

6. Exposure Doses – Determination of the minimal erythemal dose on protected skin (MED(PS)) is described in § 352.73(c) of the SPF testing procedures: "A series of seven exposures shall be administered to the protected test sites to determine the MED of the protected skin (MED(PS)). The doses selected shall consist of a geometric series of five exposures, where the middle exposure is placed to yield the expected SPF plus two other exposures placed symmetrically around the middle exposure." The agency proposed this format in the OTC sunscreen tentative final monograph (58 FR 28194 at 28269 to 28272), in the context of SPF values up to 30, because of its concern that a widely-spaced geometric progression offers less accuracy and precision in the upper SPF ranges and may produce overestimation of the true SPF. Exposure dose intervals in the above geometric series decrease as expected SPF values increase.

The Division would appreciate your comments and any supporting data concerning the adequacy of the current exposure dose format in the testing of sunscreen drug products claiming to have SPF values over 30.

7. Labeling - In the sunscreen final rule (64 FR 27666 at 27675), the agency stated that the nonlinearity (i.e., percent reduction in erythemogenic ultraviolet radiation) of the SPF rating system is a concept difficult to explain in the limited space on a product label. The agency further noted the relatively small difference in additional sunburn protection for most people provided by SPF 30 and SPF 50 sunscreens in terms of their absorption of erythemal ultraviolet radiation. Our concern remains the consumer's perception and understanding of the difference in screening abilities between, for example, an SPF 4 and SPF 15 as opposed to an SPF 30 and SPF 50.

We are concerned that an average sunscreen consumer may ascribe more to high SPF values than is clinically relevant and that such products may further encourage the use of sunscreens as a safe way to prolong sun exposure. The concept of increasing SPF values has been described in the context of increasing the time for which a person could be exposed to the sun without burning. While such a description may be true, it omits essential information about skin cancers and photoaging that may occur from different (i.e., nonerythemogenic) wavelengths and/or at

suberythemal doses of ultraviolet radiation in the erythemogenic wavelengths. Further, sunscreen use alone will not prevent all of the possible harmful effects of the sun for all consumers, even with the use of high-SPF sunscreen products. Variation between individuals, ultraviolet radiation absorption and substantivity of sunscreen products, exposure conditions, and conditions of use (e.g., inadequate application/reapplication) preclude a precise result for each individual. Sunscreens are part of a sun protection program in which it is clear that the goal is to limit sun exposure even with the use of a sunscreen. Without adequate labeling, high SPF numbers may dilute the desired public health message.

Labeling comprehension data submitted by the CTFA that was discussed at our February 11, 1997 public feedback meeting (Docket 78N-0038, Comment MM14) indicated a fair amount of confusion concerning consumer comprehension of the SPF rating system. The Division would appreciate receiving your feedback on any proposed methods for communicating in labeling the level of sun protection associated with high-SPF sunscreen drug products.

Also, much of the concern expressed at our July 22nd meeting about the labeling of high SPF values concerned limitations on product selection advice given by health professionals to particularly sun-sensitive patients. In addition to the information requested above, we are also interested in receiving your comments relative to the use of professional labeling specifically to provide high-SPF value information to health professionals.

Conclusion

In summary, we believe that the OTC sunscreen final rule addresses issues that the agency has determined can be finalized based on scientific considerations and that it will benefit consumers by providing clear, informative required labeling for sunscreen products offering sunburn protection and labeled with SPF claims. In addition, this rulemaking will ensure that all sunscreen products making SPF claims will be tested prior to marketing. These requirements will allow consumers access to improved, comprehensive information, so that they can more easily compare products and make better personal sunburn protection and prevention choices.

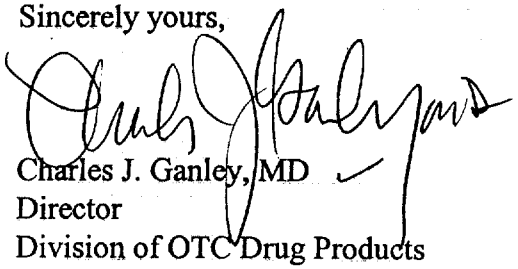
We are interested in your feedback on the concerns addressed in this letter. Upon the submission and review of adequate data to support the testing of high-SPF sunscreen drug products, along with sufficient data that this information can be adequately communicated in consumer labeling, the agency will take appropriate action. All other suggestions received by the agency concerning SPF test procedures (i.e., those not necessarily affecting the testing of only high SPF products) will also be addressed.

You also requested a follow-up working meeting to further discuss your major concerns, at our July 22nd meeting. You identified "anti-aging and related claims" and "make-up products with sunscreens" as two other major issues ("trade dress" of drug-cosmetic products was discussed at

our meeting of August 24, 1999). Please contact our office (Elizabeth Yuan at 301-827-2222) as soon as possible to arrange for a follow-up meeting to exchange viewpoints on these issues and to provide the requested information and data concerning high-SPF testing and consumer understanding of high-SPF labeling.

We appreciate your cooperation in these matters and look forward to further dialogue in the future.

Sincerely yours,



Charles J. Ganley, MD
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research